Docket No. BULK 3.0-045

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:
Manne Satyanarayana REDDY, et al.

Application No.: 10/809,192

Filed: March 25, 2004

For: CRYSTALLINE CETIRIZINE MONOHYDROCHLORIDE

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL

Dear Sir:

Applicants have claimed priority under 35 U.S.C. § 119 from an application that was filed in India. Accordingly, a certified copy of the application identified as 252/MAS/2003 is enclosed herewith to complete the priority claim requirement.

If any additional issues remain to be addressed in connection with the filing of this application, please contact the undersigned.

Respectfully submitted,

Robert A. Franks
Attorney for Applicants
Reg. No. 28,605

April 4, 2007

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Attorney Docket No.: BULK 3.0-045

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Application No.: 10/809,192
Filing Date: March 25, 2004
First Inventor: Manne Satyanarayana REDDY
Art Unit: 1624

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Joan Anisiewski
Typed or printed name of person signing Certificate

Registration Number, if applicable

908-203-4953
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper. Documents enclosed:

Transmittal Letter (1 pg)
Certified Copy of India App. No. 252/MAS/2003 (18 pgs.)
Post Card Receipt

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy
Application, Complete Specification, Abstract & Drawings of t
extract of Patent Application No.252/MAS/2003, dated 25/03/2003
M/s. Dr. Reddy's Laboratories Limited, having its registered office
7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....In witness there

I have hereunto set my han

Dated this the 27th day of July 20

M.S. V

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Desig

PAT T ICE BRANCH
GOV NT OF INDIA
Guna m k, 6th Floor, Annex.II
No.44 Ar Salai, Teynampet, Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare -that

1. (a) we are in possession of an invention titled"Novel crystalline form of [2-[4-[(4-Chlorophenyl)-phenylmethyl]-1-piperazinyl] ethoxy] acetic acid hydrochloride(Cetirizinemonohydro chloride) and process for the preparation thereof."
   (b) that the Provisional/Complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to me/us.
2. further declare that the inventor(s) for the said invention are **Manne Satyanarayana Reddy, Srinivasan Thirumalai Rajan, Uppala Venkata Bhaskara Rao and Konda Srinivasa Reddy.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. We claim the priority from the application(s) filed in convention countries,particulars of which are as follows.
4. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee
5. We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.
6. That We are the assignee or legal representative of the true and first inventors.
7. That our address for service in India is as follows:

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P.- 500 016

8. Following declaration was given by the inventor(s) or applicant(s) in the convention country:
9. We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

252/MAS/2003

(Signed)_____

Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda, Hyderabad-500 038.

(Signed)_____

Srinivasan Thirumalai Rajan,
Plot No. 12,
Lake view Enclave,
Miyapur,
Hyderabad-500 050.

Signed)_____

Uppala Venkata Bhaskara Rao,
MIG-53,
Dharma Reddy Colony,
Kukat Pally,
Hyderabad-500072.
Andhra pradesh,
India.

(Signed) K. Srinivasa Reddy

Konda Srinivas Reddy ,
Gorojavolu gunta palem(village),
Abbinene gunta palem(post),
Peda nandhi padu(mandal),
Guntur(dist),
Andhra pradesh,
India.

10. That to the best of my/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application.

11. Following are the attachments with the application
    (a) Complete specification (---10 pages, in triplicate)
    (b) Drawings (---03 pages, in triplicate)
    (c) Priority documents(s)
    (d) Statement and Undertaking on Form-3.
    (e) Power of authority
    (f) Abstract of the invention (---01- page, in triplicate)
    (g) Fee Rs. 5000.00 (five thousand rupees only) in cheque bearing No. 337050 dated 07.03.2003 drawn on HDFC Bank Limited, Lakdi-kapul, Hyderabad – 4.

We request that a patent may be granted to me/us for the said invention.

Dated this 25th day of March 2003.

(Signed)

Dr.Manne Satyanarayana Reddy
Vice president (R&D),
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

252/MAS/2003

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

Novel Crystalline Form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride) and process for the preparation thereof.

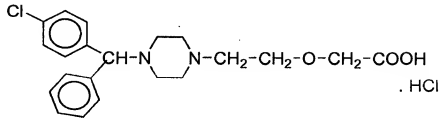
Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to novel crystalline form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride. [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid is also known Cetirizine. Cetirizine dihydrochloride salt is marketed under brand name "Zyrtec" in Europe market.

The present invention also relates to the process for the preparation of novel crystalline form of Cetirizine monohydrochloride, which can be depicted as Formula (1).



Formula (I)

BACKGROUND OF THE INVENTION

Cetirizine is used for the treatment of allergic syndromes such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria etc. The product was proved to be remarkably free from side effects on the central nervous system.

US 4,525,358 discloses Cetirizine dihydrochloride having the melting point of 225°C . The said patent also discloses the process for the preparation of Cetirizine dihydrochloride.

Many of the related patents were disclosed the process for the preparation of Cetirizine and its salts including dihydrochloride in various methods, but none of these patents were described the crystalline form of Cetirizine monohydrochloride of the present invention.

During our laboratory experimentation as a part of process development, novel crystalline form of Cetirizine monohydrochloride was resulted while crystallizing the Cetirizine in different solvents.

Hence, the main aspect of the present invention is to provide novel crystalline form of Cetirizine monohydrochloride.

The aspect of the present invention is to provide the novel crystalline form of Cetirizine monohydrochloride and process for the preparation thereof.

The novel crystalline form of Cetirizine monohydrochloride was characterized by X-ray powder diffractogram, which has the well-resolved peaks.

The processes of the present invention are simple, eco-friendly and easily scalable.

SUMMARY OF INVENTION

The present invention relates to the novel crystalline form of Cetirizine monohydrochloride and the process for their preparation there of.

The process for the preparation of crystalline form of Cetirizine monohydrochloride comprises dissolving Cetirizine dihydrochloride in water, basifying with alkali and washing with a solvent. After adjusting the pH of the aqueous part to 2-4 preferably 2-3 and extracting the Cetirizine monohydrichloride into a solvent. Upon distillation of the solvent isolating the crystalline Cetirizine monohydrochloride with acetone.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig-1 is a diagram showing the X-ray powder diffraction of crystalline form of Cetirizine monohydrochloride.

Fig-2 is a diagram showing the infrared pattern of crystalline form of Cetirizine monohydrochloride.

Fig-3 is a diagram showing the differantial sccaning calorimetry of crystalline form of Cetirizine monohydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel crystalline form of Cetirizine monohydrochloride. The present invention also provides a process for preparing novel crystalline form of Cetirizine monohydrochloride.

The present invention of crystalline form of Cetirizine monohydrochloride was characterized by melting point between 183-189°C, endotherm peak around 186°C by differential scanning calorimetry and by X-ray powder diffractogram. The X-ray powder diffraction pattern of crystalline form of Cetirizine monohydrochloride was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source. The differential scanning calorimetry was measured on a perkin elmer.

The present invention is to prepare novel crystalline form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride), which comprises;

a. dissolving or suspending the [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid or salts thereof in water and then basifying to pH of 8 – 14 preferably to 12 with a suitable inorganic bases like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or its bicarbonates etc. preferably sodium hydroxide.

b. adjusting the pH of the aqueous solution to 2-4 preferably 2-3 with hydrochloric acid

c. extracting the compound into a suitable organic solvents such as dichloromethane, chloroform, ethylacetate, etc. preferably dichloromethane;

d. drying the organic solvent with sodium or magnesium sulphates preferably sodium sulphate;

e. distilling off the solvent at a temperature of 25-100^{O}C; with or without using vacuum preferably using vacuum.

f. dissolving the residue in keto solvents such as acetone, ehtyl methyl ketone and methyl isobutyl ketone preferably acetone.

g. stirring the solution at 25-35°C for compound separation.

h. finally isolating the solid by filtration and washing with the same solvent;

i. drying the compound at a temperature of 40 – 120°C preferably 50-60°C to afford the desired crystalline form of 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl]ethoxy]acetic acid hydrochloride (Cetirizine monohydrochloride) of the formula-1.

The novel crystalline form of the present invention is characterized by X-ray powder diffractogram.

The X-ray powder diffraction pattern of crystalline form of Cetirizine monohydrochloride is having well-resolved peaks, which indicates the formation of an crystalline form.

The 2-theta values and their intensity percentages of relevant peaks in X-ray powder diffraction pattern of crystalline form of Cetirizine is shown in the Table-1.

Table-1.

2-Theta Value (°)	Intensity, I/I_O (%)
12.968	100.0
22.941	98.1
20.405	59.1
17.348	57.5
19.148	54.3
8.749	41.5
14.189	39.4
17.01	37.9
28.28	27.6
21.610	22.1
9.842	21.4

The crystalline form of Cetirizine monohydrochloride of the present invention is having the X-ray powder diffractogram pattern substantially as depicted in Figure (1).

The process for the preparation of crystalline form of Cetirizine monohydrochloride is simple, eco-friendly and commercially viable. Alternatively the crystalline form of Cetirizine monohydrochloride can also be prepared from the crude Cetirizine obtained by hydrolysis of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetamide. And also the said crystalline form may be prepared by crude Cetirizine obtained by the condensation of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethanol with sodium monochloro acetate.

It is noteworthy to mention that the process of the Cetirizine or its pharmaceutical acceptable salts was disclosed in prior art references known in the art. Cetirizine or its pharmaceutical acceptable salts including dihydrochloride can also be outsourced in commercial quantities.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Example-1: Preparation of novel crystalline form of Cetirizine monohydrochloride from Cetirizine dihydrochloride:

Cetirizine dihydrochloride (150 grams) was dissolved in water (1500 ml) then basified to pH 12 using sidium hydroxide. Again pH is adjusted to 2-3 using hydrochloric acid and extracted the product into dichloromethane (2 X 450 ml). The resultant organic layer washed with water (2X150 ml) and dried with sodium sulphate. Distilled off the solvent under reduced pressure. To the residue added 300 ml of acetone and distilled off acetone completely. Then added acetone 900 ml and stirred at 40 – 45°C upto free compound separated out. Filtered the compound and washed with acetone (150 ml) and dried at 50 – 60°C to get the crystalline form of Cetirizine monohydrochloride.

(Weight: 87.5 grams) Melting point 183 – 189°C.

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig.1 is a characteristic X-ray powder diffraction pattern of novel crystalline Form of 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride) .

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The significant 2-theta values are 8.749, 9.842, 12.968,14.189, 17.01,17.348,19.148, 20.405, 21.610, 22.941and 28.28 two-theta degrees.

Fig.-2.is infrared pattern of novel crystalline Form of 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl]ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride).

Fig.-3 is Differential Scanning Calorimetry thermogram of novel crystalline Form of 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride) The Differential Scanning Calorimetry thermogram exhibits a significant endo-exo pattern respectively at $186^{O}C$ and $260^{O}C$.

We claim:

1. A novel crystalline form of Cetirizine monohydrochloride and the process for the preparation thereof which comprises,

a. dissolving or suspending the [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid or salts thereof in water and basifying to pH of 8 – 14 preferably to 12 with a suitable inorganic bases like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or its bicarbonates etc. preferably sodium hydroxide.

b. adjusting the pH of the aqueous solution to 2-4 preferably 2-3 with hydrochloric acid;

c. extracting the compound into a suitable organic solvents such as dichloromethane, chloroform, ethylacetate, etc. preferably dichloromethane;

d. drying the organic solvent with sodium or magnesium sulphates preferably sodium sulphate;

e. distilling off the solvent at a temperature of 25-40^{O}C; with or without using vacuum preferably using vacuum.

f. dissolving the residue in keto solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone etc. preferable acetone;

g. stirring the solution at 25-35°C for compound separation.

h. finally isolating the solid by filtration and washing with the solvents mentioned in step (f)

i. drying the compound at a temperature of 40 - 120°C preferably 50-60°C to afford the desired crystalline form of 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride (Cetirizine monohydrochloride) of the formula-1.

2. A novel crystalline form of Cetirizine monohydrochloride having the x-ray powder difraction as mentioned in figure-1.

3. A novel crystalline form of Cetirizine monohydrochloride having the melting point at the range of 183-189°C.

4. A novel crystalline form of Cetirizine monohydrochloride having the diffrantial scanning calorimetry as shown in figure-2.

5. A novel crystalline form of Cetirizine monohydrochloride having the infrs red ptern as shown in figure–3.

6. A novel crystalline form of Cetirizine monohydrochloride and the process for the preparation thereof substantially herein described and examplified.

Dated this 10th day of March 2003

Signed)

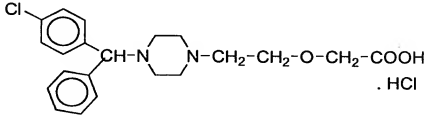
Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr.Reddy's Laboratories Limited.

ABSTRACT

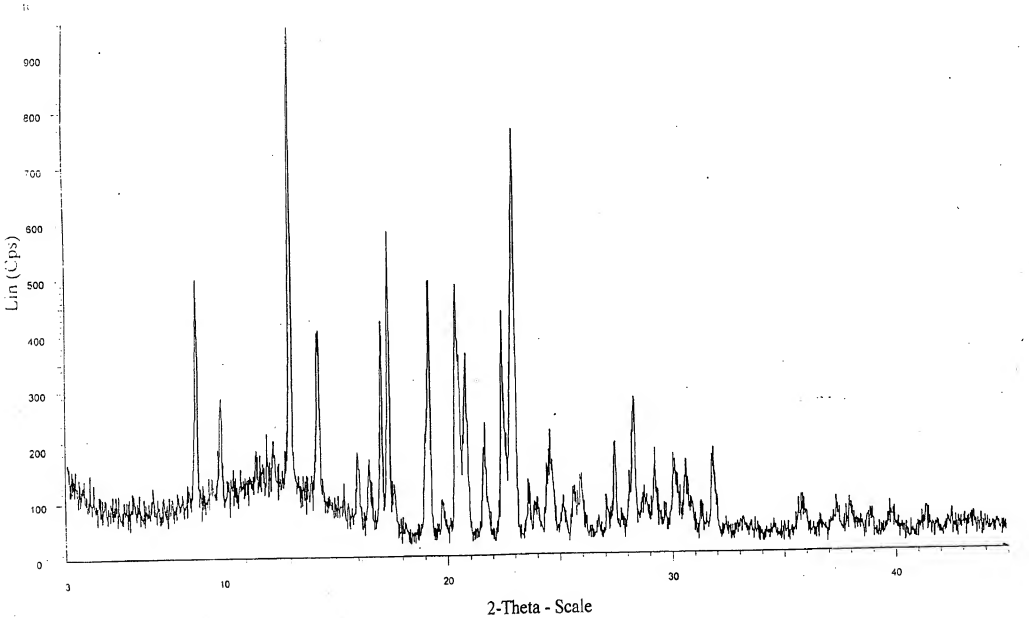
Title of the invention : "Novel Crystalline Form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid hydrochloride ·(Cetirizine monohydro chloride) and process for the preparation thereof ".

The present invention relates to the novel crystalline form of Cetirizine monohydrochloride and the process for their preparation there of.

The process for the preparation of crystalline form of Cetirizine monohydrochloride comprises dissolving Cetirizine dihydrochloride in water, basifying with alkali and washing with a solvent. After adjusting the pH of the aqueous part to 2-4 preferably 2-3 and extracting the Cetirizine monohydrichloride into a solvent. Upon distillation of the solvent isolating the crystalline Cetirizine monohydrochloride with acetone. Cetirizine monohydrochloride can be dipected as Formula-1.

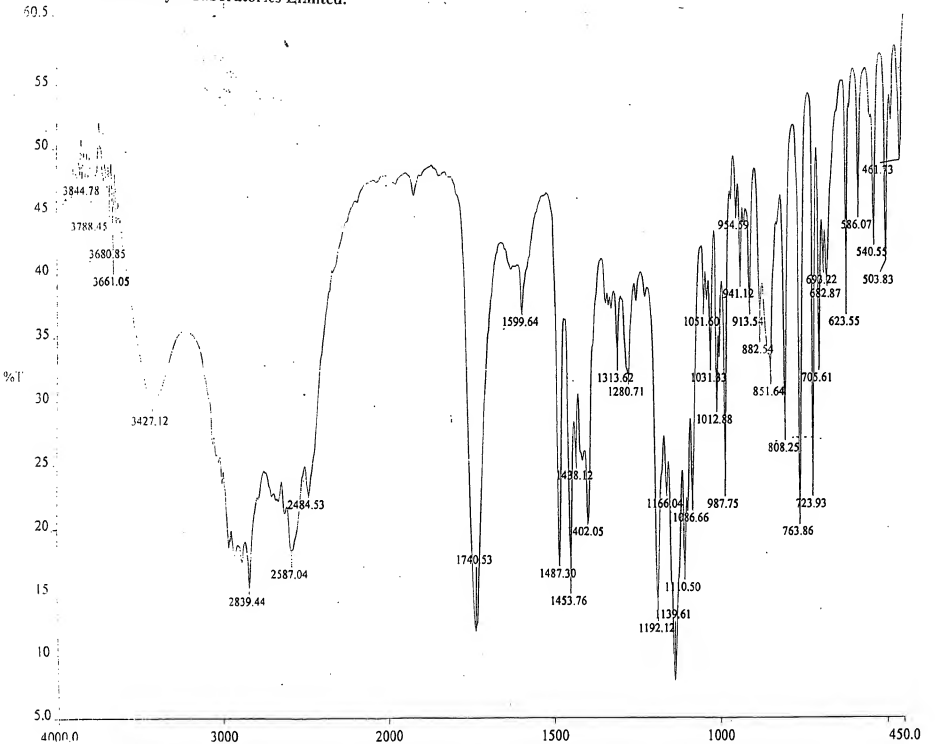


Formula- I



Dr. Manne Satyanarayana Reddy.

Dr. Reddy's Laboratories Limited.



Dr. Manne Satyanarayana Reddy.

Dr. Reddy's Laboratories Limited.

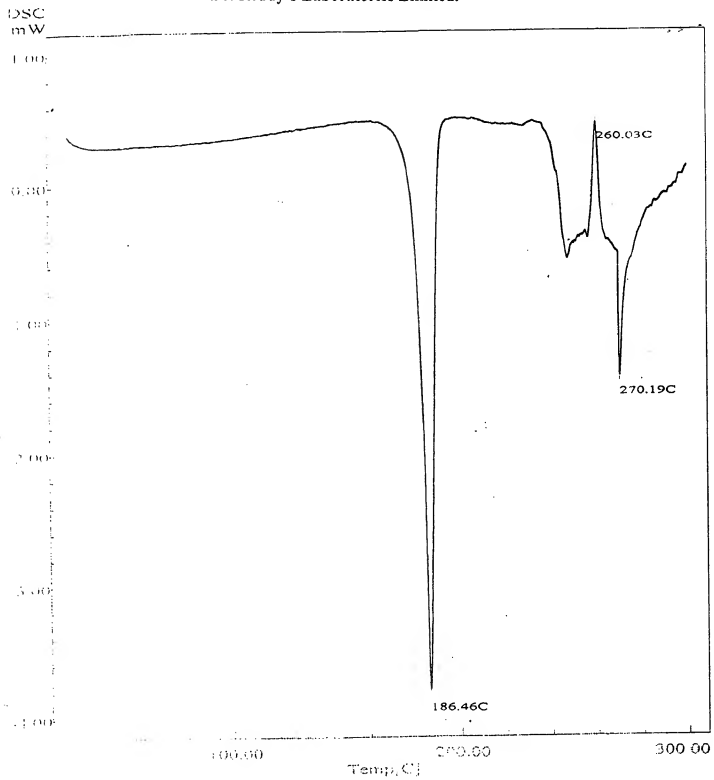


Figure 3 of 3

Dr. Manne Satyanarayana Reddy.